Similar but different: the case of metoprolol tartrate and succinate salts

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ABSTRACT The solid-state structure and behavior of tartrate (**MT-o**) and succinate (**MS-m**) metoprolol salts have been studied with a combined experimental (XRD by both single crystal and microcrystalline powder and DSC) and modeling approach (MD and MO calculations). In

spite of their close similarity at the molecular level in the corresponding crystal lattices, calorimetric data suggest for **MS-m** a slight greater cohesive energy. In addition and more importantly, they show significantly different "macroscopic" behaviors: **MS-m** undergoes a reversible anisotropic lattice expansion/contraction upon temperature change and once melted quickly re-crystallizes to the starting crystal phase. On the other hand, **MT-o** expands/contracts isotropically, and upon cooling from the melt gives an amorphous solid, which, at ambient conditions, takes six days to completely revert to the starting crystal form. Both findings are relevant in the field of the pharmaceutical drug development, i.e. when the phase purity of these APIs is assessed, discussed and possibly related to drug product formulations and manufacturing methods.

Introduction

It is well known that several physical and chemical properties such as solubility, dissolution rate, melting point, density and chemical reactivity of an active pharmaceutical ingredient (API) can affect its processability and quality.[1] Given that most of the above-mentioned properties depends on the crystalline structure of the API,[2,3] the study of its solid state forms and of their behavior under certain storage conditions, is essential when dealing with pharmaceutical compounds.

In addition, although the most stable form of an API is usually employed in formulations, sometimes it may be convenient to use a metastable form in order to enhance its bioavailability. As a consequence, the knowledge of the relative polymorphic stability under defined conditions of temperature and pressure assumes a crucial role.

Bearing in mind what is stated above and considering that solid-solid transformations, e.g. phase transformations, solvation/desolvation processes as well as chemical reactions, can occur in response to variations in environment (temperature, ambient/vacuum pressure, humidity), manufacturing, storage, or simply over time, monitoring the API behavior under different experimental conditions appears to be essential.[4]

In this context, spectroscopy, X-ray diffraction, both from single-crystal (SCXRD) and microcrystalline powder (XRPD), solid state NMR, thermal analysis (in particular differential scanning calorimetry, DSC), microscopy and molecular modeling are commonly used as interdisciplinary tools for characterizing pharmaceuticals, including APIs and formulations.[5,6,7] Indeed, these techniques provide insights on the molecular and crystal structure of the solid forms, their phase distribution, their transformations, the heats and temperatures related to phase transitions, solvation/desolvation processes and decomposition.[8,9] Moreover, computational methods can provide a plethora of complementary information (molecule's conformational space, molecule's potential energy surface, role of intra- and/or inter-molecular interactions in driving the 3D arrangement of molecules having a large number of degrees of freedom, etc.) useful to rationalize the solid state results.[10]

Herein we report a solid state study on the succinate and tartrate metoprolol salts (**MS** and **MT**, hereafter). Metoprolol, (±)-1-isopropylamino-3-[4-(2-methoxy-ethyl)-phenoxy]-propan-2-ol (Scheme 1), belongs to the class of β_1 selective β-adrenoreceptor blocking drugs,[11] and is widely used to treat heart failure and cardiovascular diseases, such as hypertension, angina, acute myocardial infarction, ventricular tachycardia, just to name a few.[12,13] Due to the fact that it has a quite low melting point (~323 K, as determined by differential scanning calorimetry, DSC)[14] and that drugs that melt below 373 K are difficult to manufacture, metoprolol is commonly

administered as succinate (**MS**, melting point around 409 K) or tartrate (**MT**, melting point around 393 K) salts. While the tartrate salt is used in immediate-release formulations, the succinate one is used in extended-release dosage forms:[15] both formulations contain the metoprolol cation and the dicarboxylate anion in a 2:1 ratio. In both cases the metoprolol molecule is present as a racemic mixture and, in **MT**, the dextrorotatory enantiomer of the tartrate anion is used. Incidentally, the cardiac β-blocking activity of metoprolol, as most of the β-blockers, resides in the S-isomer.[16]

MS and **MT** have been the subject of numerous studies mainly related to pharmaceutical technology,[17,18,19] clinical pharmacology,[20,21] pharmacokinetics,[22,15] spectral,[23] thermal[24] and structural characterization.[14,25,26] In particular Ionescu and coworkers[14] have investigated **MT** by single crystal and powder X-ray diffraction, hot stage microscopy and DSC. As for the solid state structure, they found that, irrespective of the different crystallization procedures employed, **MT** always crystallizes in the space group $P2_1$ (hereafter this crystalline form will be referred to as **MT-m**), whose asymmetric unit comprises a pair of 2:1 metoprolol cations and *dextro*-tartaric acid anion. Finally, the XRPD pattern computed from the single crystal data (collected at 173 K) is in keeping with the experimental one and agrees well with that already reported by Luch.[25] In other words, results reported by Ionescu[14] and Luch[25] refer to the same crystalline form of the salt, namely **MT-m**. As for the succinate salt, the solid state structure from single crystal X-ray diffraction at 200 K (monoclinic crystal system, **MS-m**, hereafter) has been reported by Di Vaira et al.[26]

The goal of the present work is to better characterize and understand the solid state behavior of such metoprolol salts under different experimental conditions [temperature, atmosphere (vacuum, air, N_2), time of storage], by using a combined experimental approach (XRD by both

single crystal and microcrystalline powder and DSC). In particular attention has been paid to possible XRPD pattern changes by applying heating/cooling cycles to the **MS** and **MT** samples. Results from thermal and XRD analyses are compared and discussed. To complete the picture, the conformational space of a metoprolol-like cation has been assessed by DFT calculations and molecular dynamics simulations.

EXPERIMENTAL SECTION

Materials and methods. Both Metoprolol succinate (**MS**) and tartrate (**MT**) salts were purchased from Sigma Aldrich (grade: primary reference standard, CAS numbers 98418-47-4 and 56392-17-7 for **MS** and **MT**, respectively) and used as received. Reagent grade solvents were used.

Single crystal X-ray diffraction (SCXRD). Numerous attempts were made to obtain single crystals of **MT** suitable for SCXRD analysis. The best crystals, even if not excellent, were obtained by slow evaporation from a 1:2 methanol:n-butanol solution. Several crystals were then tested by X-ray diffraction and the best one was utilized for the data collection. Single crystal diffraction measurements were carried out at 100 K, with an Oxford Diffraction Excalibur diffractometer using a Cu-K_α radiation (λ = 1.54184 Å). Data collection was performed with the program CrysAlis CCD.[27] Data reduction was carried out with the program CrysAlis RED (CrysAlis RED, 2006).[28] Absorption correction was performed with the program ABSPACK in CrysAlis RED. The metoprolol tartrate salt crystallizes in the orthorhombic crystal system, space group $P2_122_1$ (this crystalline form hereafter will be referred to as **MT-o**).

The structure was solved by using the SIR-97 package[29] and subsequently refined on the F^2 values by the full-matrix least-squares program SHELXL-97.[30]

Geometrical calculations were performed by PARST97,[31] and molecular plots were produced by the programs ORTEP-3,[32] Mercury (v3.5)[33] and Discovery Studio Visualizer (v2.5.5.9350).[34] All the hydrogen atoms were included in geometrically generated positions and refined in agreement to the atoms to whom they are bonded, although the two ammonium and the hydroxyl H atoms of the two metoprolol cations could be clearly identified in difference Fourier maps. All the non-hydrogen atoms were refined anisotropically.

The correct absolute structure was chosen on the basis of the chirality of the naturally occurring form of tartaric acid [*i.e.* L-(+)]. In table 1 crystal data and refinement parameters of **MT-o** are reported.

X-ray microcrystalline powder diffraction (XRPD). XRPD measures were carried out at room temperature in air by using a Bruker New D8 Da Vinci diffractometer (Cu-Kα radiation, 40 kV x 40 mA), equipped with a Bruker LYNXEYE-XE detector, scanning range 2θ = 3-50°, 0.02° increments of 2θ and a counting time of 0.8 s/step.

In order to determine the crystal parameters of **MT** at room temperature, a scan was performed in capillary, followed by the Pawley fit with the software TOPAS.[35] A shifted Chebyshev with 8 coefficients and a pseudo-Voigt function were used to fit background and peak shape, respectively. Refinement converged with R_{wp} = 7.23 but the diffractogram shows the presence of two spurious peaks (2θ = 17.5, 19.6°) not assigned to any phase (see figure S1).

Temperature-resolved experiments (performed in triplicates) were carried out: 1) in vacuum in the range 173-303 K and in air (range 303-413 K) by using a Bruker D8-Advance (Cu-Kα

radiation, 40 kV x 40 mA) equipped with a multi-channels energy dispersion detector (SOLX) and a MRI (Material Research Instruments) heating stage for temperature-dependent measurements. Scanning range 2θ = 3–50°, 0.02° increments of 2θ and with a 1 s/step counting time; 2) under nitrogen in the range 303-420-303 K with an Anton Paar HTK 1200N hot chamber mounted on a Panalytical XPERT PRO diffractometer (Cu-Kα radiation, 40 kV x 40 mA), equipped with the PIX-CEL solid state fast detector. Scanning range 2θ = 3–50° with a 1 s/step counting time and 0.03° increments of 2θ.

In all cases the temperature variation rate was 10 K/min, after the target temperature was reached the sample was kept 10 minutes at that temperature before proceeding with data collection.

Finally, cell parameters at different temperatures were obtained with the same procedure described above.

Differential Scanning Calorimetry (DSC). Differential scanning calorimetry (DSC) experiments were carried out using a Mettler Toledo DSC1 Excellence. Measures were run in sealed aluminum pans (mass samples range from 1 to 6 mg). Temperature and enthalpy calibration were done using indium as a standard. Melting point (Tm) and heat of fusion (ΔH) of metoprolol tartrate were determined by measurements in the 300-410-300 K range, while for metoprolol succinate experiments were performed in the 300-430-300 K range. In all cases a linear heating rate of 5 K/min was used. Experiments were carried out under nitrogen (the flow rate of dry nitrogen gas was 70 mL/min) as well as in air. DSC peaks were analyzed using the STAR^{e} software.[36] The melting data reported were the average of two measurements, standard errors were ±0.1 K for temperature and ±0.3 kJ/mol for enthalpy.

Molecular Modeling. Geometry optimizations (MM) and molecular dynamics (MD) simulations were performed on **BS_aT**, **BS_TG$^-$** and **BS_TG$^+$** as representatives of the three conformational families identified by the solid state structure survey (details in the Result and discussion section). All calculations were made by using the CHARMm Force Field.[37] MM calculations were performed on each species by using the Smart Minimizer energy minimization procedure implemented in Accelrys Discovery Studio 2.1[34] and before starting the MD simulations, the geometry of each compound was further optimized using the steepest descent and conjugate gradient algorithms. MD simulations were carried out at 100 and 300 K, both in vacuum as well as in an implicit water model; water calculations were performed mimicking the solvent by using a distance-dependent dielectric constant of 80. In the molecular dynamics simulations, the time step was 1 fs for all runs, equilibration time = 100 ps and production time = 1000 ps, snapshot conformations were sampled every 10 ps. The programs used for the MD and the energy minimization were the Standard Dynamics Cascade and Minimization protocols, trajectories were analyzed by the Analyze Trajectory protocol, all implemented in Discovery Studio 2.1.

GAUSSIAN09 (Rev. C01)[38] was used for molecular orbital (MO) calculations using the following functionals: B3LYP[39,40] and B97D.[41] The basis set was 6-31+G(d,p).[42] The Berny algorithm was used.[43] The reliability of the stationary points was assessed by the evaluation of the vibrational frequencies. Geometry optimizations were performed on the three conformational isomers **BS_aT**, **BS_TG$^-$** and **BS_TG$^+$**.

RESULTS AND DISCUSSION

Single crystal X-ray diffraction and modeling studies. The metoprolol tartrate salt crystallizes in the orthorhombic crystal system, space group $P2_122_1$ (**MT-o**). In the asymmetric unit each of the enantiomers of the metoprolol and two halves of the tartrate anion are present.[44] In figure 1 an ORTEP-3 representation of the two cations is reported. The two independent cations of metoprolol in the asymmetric unit are related by a pseudo-mirror plane, as depicted in figure 2, where the superimposition of the R enantiomer and of the mirror plane-image of the S one is reported. Due to the presence of this pseudo-mirror (that has been observed in **MT-m** too[45]), and considering that the S enantiomer has a cardiac β-blocking activity significantly higher than the R one,[46] in the following attention will be focused on the S-isomer.

A survey of the Cambridge Structural Database (CSD, v. 5.36, February 2015)[47] gives eleven compounds featuring the molecular fragment sketched in scheme 2a.[48] As for the charged species, on the basis of the dihedral angles characterizing the conformation of the chain bearing the isopropyl group (*i.e.*: C6-C1-O1-C7, C1-O1-C7-C8, O1-C7-C8-C9, C7-C8-C9-N1, see figure 1),[49] two main conformational families can be recognized: an elongated conformation (*all-trans*, **aT** hereafter), observed in the structure with Refcode JIRWIR[50] and in **MT-o** and a more compact disposition (gauche about the C7-C8 bond, hence *ttgt* family) as in **MS-m**[26] (*vide infra*), in CIMJUD,[51] in QAJYIL and in DETHIU.[52,53] The second family can be further divided into two groups depending on the sign of the gauche dihedral angle about the C7-C8 bond: negative in **MS-m** and CIMJUD (*ttg*$^-$*t*, **TG**$^-$ hereafter) and positive in DETHIU and QAJYIL (*ttg*$^+$*t*, **TG**$^+$ hereafter). These folded conformations feature a weak[54] $CH_2\cdots O$ intra-molecular H-bond (C9-H$\cdots$O1 distances and angles range from 2.3 to 2.5 Å and from 98 to 114°, respectively) forming a five-membered ring that could contribute to stabilize the **TG** families.

In the neutral species (^{i}Pr-amine tail) four major[44] kinds of conformational isomers can be recognized.

This is well illustrated in figures 3 and 4, which show the superimposition of the X-ray structures of the cationic and neutral species. Finally, when neutral and charged species are considered all together they grouped in five distinct families: the most representative is the *all trans* one that encompasses the conformation found in **MT-o** (figure 5).

Moreover, a special comment deserves the molecular structure of the metoprolol in the strictly related **MT-m**[14] and **MS-m**[26] salts. As for **MT-m**, the metoprolol cation shows a conformation very similar to that found in **MT-o** (see table 2 for a comparison of the torsion angles defining the 3D arrangement of the phenyl side arms in the S enantiomers).[45] On the contrary, the metoprolol cation overall shape in **MS-m** differs from that observed in **MT-o** (see figure 6 and table 2), due to the torsions about the C7-C8 bond of the ^{i}Pr chain (g^{-} or –synclinal in **MS-m** and *t* or antiperiplanar in **MT-o**) and the C13-C4 bond of the 2-methoxyethyl chain (g^{+} or +synclinal in **MS-m** and -anticlinal in **MT-o**).[55]

In summary, the solid state data show at least three different conformations for the positively charged tail (figure 3), while for the methoxy chain two different 3D-arrangements were found (figure 6).

Given that metoprolol shares the 2-hydroxy-3-isopropylaminopropoxy group with other β-adrenoreceptor blocking agents, such as, for instance, atenolol, practolol, pindolol and bisoprolol, it might be of some interest to get an idea of the conformational behavior of such a tail by investigating the basic structure (**BS**, see scheme 2b) common to all the above mentioned β-adrenoreceptor antagonists by Molecular Dynamics (MD) and MO (DFT) methods.

The **BS_aT**, **BS_TG$^-$**, and **BS_TG$^+$** conformers, representative of the three conformational families (*all trans, ttg$^-$t* and *ttg$^+$t*, respectively) identified by the solid state structure survey above discussed, were then used as starting points for MD simulations performed at 100 and 300 K, both in vacuum as well as in an implicit water model. Notwithstanding the starting isomer (**BS_aT**, **BS_TG$^-$**, and **BS_TG$^+$**), the large majority of the conformations collected at 300 K in vacuum shows a "doubly-folded" arrangement (which is completely different from those observed in the solid state, figures S2-S4) about the C7-C8 and C8-C9 bonds stabilized by a strong intramolecular H-bond[50] between the ammonium grouping and the oxygen atom O1 (mean $NH_2^+\cdots O$ distance 2.0 Å). The different conformational preference in vacuum with respect to the solid state is not surprising if considering that the crystal lattice is held together by strong intermolecular H-bonds between the ammonium and the hydroxyl groups of the cation and the counterions (*vide infra*), which most probably drive the arrangement of the charged side arm. The inclusion of a distance dependent dielectric constant makes the intramolecular interactions almost completely vanish in MD simulations performed at the same temperature and in most cases the charged tail adopts an elongated conformation (figures S5-S6) very similar to that found in the crystal structures of **MT-o** and **MT-m**, thus supporting the above reasoning. Finally, at 100 K the side arm bearing the isopropylammonium group remains trapped within a limited region of the conformational space close to the starting rotational isomer, both in vacuum and with an implicit water model, thus suggesting that the solid state arrangement of the charged tail corresponds to locally stable conformations. This result parallels the outcomes from DFT calculations: the optimized structures of the three conformational isomers (**BS_aT**, **BS_TG$^-$**, and **BS_TG$^+$**) do not significant differ from the input ones; in addition, they are essentially isoenergetic (max ΔG_{298}= 0.8 kcal/mol).

Summing up the solid state and modeling data, the chain bearing the isopropyl group is able to adapt to the surroundings (in vacuum and in implicit water model as from MD at 300 K and solid state data); its conformational space comprises at least three local minima (MD at 100 K and DFT data), separated by a quite low energy barrier (MD data at 300 K) given that during a MD run the energy barriers that can be easily overcome are on the order of one to two RT.

As said before, metoprolol and tartrate ions are held together in the crystal packing of **MT-o** thanks to several strong hydrogen bonds[54] (see table 3). Due to these interactions, each metoprolol cation interacts with two different tartrate anions and, at the same time, each tartrate anion interacts with four metoprolol cations (two R and two S, figure 7A). This net of H-bonds gives rise to chains, along the *c*-axis direction, formed by alternating R and S metoprolol cations, bridged by the carboxylate oxygen atoms of the tartrate. Moreover, due to the dicarboxylic nature of the tartrate, couples of metoprolol chains are held together through the anion (see figure 7B). As for the hydroxyl groupings of the tartrate anions, they are not involved in any intermolecular contact, on the contrary they form intramolecular H-bonds with the carboxylate oxygen atoms (details in table S1). Further weak interactions of CH···O type (see table 3) take place between the facing methoxyethyl side arms of two adjacent metoprolol chains along the *a* axis (see figure 8). Finally, weak hydrogen bonds involving the ^{i}Pr chain (see table 3) propagate the metoprolol-tartrate interactions along the *b* axis.

As for **MT-m**, Ionescu and coworkers describe "an infinite series of H-bonded rings and chains" held together by strong hydrogen bonds involving the carboxylate oxygen atoms of the tartrate anion and the ammonium and hydroxyl hydrogen atoms of the metoprolol cation. As mentioned above, in the orthorhombic phase described herein (**MT-o**), the metoprolol cation displays a molecular structure almost identical to that of the monoclinic phase (**MT-m**) reported

by Ionescu. As a consequence, we wonder if this could be a case of an isostructural polymorphism.[56,57] However, from the published data[14,48] it is not possible to have a clear picture of differences and/or similarities in the supramolecular arrangement of the two solids.

It is worth noting that in the strictly related **MS-m** compound, the pattern of strong hydrogen bonds (see table 3 for a direct comparison) which holds together cations and anions is quite similar to that found in **MT-o**: each metoprolol cation forms H-bonds to two anions and each succinate accepts H-bonds from four distinct cations thanks to its carboxylate groupings (see table 3). Similarly to **MT-o**, ribbons of H–bonded ions form along the *c* axis (see figure 9), while, at variance, no further significant intermolecular interactions are present, except for two C-H···π weak interactions[54] that propagate the intermolecular contacts along the *b* axis (see table 3). At the same time, such interactions, due to the mutual disposition of the ribbons, interconnect them also along the *a* axis, as evidenced in figure S7 (top).

In summary **MS-m** and **MT-o** show a close similarity at crystal level in terms of strong metoprolol-counterion interactions [number, type (H-bond donor and/or acceptor) and geometry (H-bond distances and angles)], as well as crystal densities (1.248 *vs* 1.242 g/cm^{3}calculated from SCXRD data collected at 200 K for **MS-m**[26] and at 100 K for **MT-o**). This observation parallels the fact that the hydroxyl groupings of the tartrate anion are not involved in any intermolecular contacts. In other words only the carboxylate oxygen atoms of both tartrate and succinate are involved in intermolecular H-bonds.

X-ray microcrystalline powder diffraction and differential scanning calorimetry analyses.

The correspondence between the crystal structure of **MT**, determined by single crystal X-ray diffraction (**MT-o**), and that of the bulk material was checked by indexing a high-resolution powder diffraction pattern collected at room temperature in capillary: it indexed to the same orthorhombic cell [cell parameters: a = 45.561(1), b = 8.4621(6), c = 9.7381(5) Å, in the $P2_122_1$ space group][58] found in the SCXRD experiment performed at 100 K.

The thermal stability of **MT-o** was then assessed by combining data from variable temperature XRPD and DSC analyses. Two sets of XRPD experiments were performed: in vacuum in the range 173 - 303 K; in air and under N_2 atmosphere in the range 303-413-303 K. Upon heating, the polycrystalline **MT-o** did not undergo any change until the melting point was reached (see figure 10). No recrystallization process was observed during the cooling step from 413 to 303 K (see figure 11). DSC measurements performed during a similar heating/cooling cycle (300-410-300 K) confirmed the previous findings: neither evidences of thermodegradation[59] nor exothermic peaks in the cooling step (see figures S8 and S9) were observed.

The amorphous sample was then left in air for four days at room temperature and a XRD powder pattern was collected every day for ten days. As evidenced in the diffractogram reported in figure 11 (top), it took four days for the recrystallization to begin and six days for the process to be completed (patterns collected from the sixth to the fourteenth day are well superimposable with each other and match the one collected at room temperature in capillary). The DSC trace of the re-crystallized sample shows a single endotherm peak at 394.7 K (extrapolated peak 394.7 K) with a melting enthalpy of 155.6 J/g (106.5 kJ/mol,). Both these values nearly exactly match those found for a fresh sample of **MT** exposed for comparative purposes to an identical

heating/cooling cycle (300-410-300 K; melting temperature: peak 395.9 K, extrapolated peak 396.2 K; melting enthalpy: 159.0 J/g, 108.8 kJ/mol.[60]

Thus the **MT-o** sample undergoes a reversible crystalline-to amorphous-to crystalline phase transition, where the thermodynamically spontaneous amorphous-to-crystalline step occurs in air over time (six days are required to achieve a complete re-crystallization) at room temperature (that is above its glass transition temperature,[61] as expected). Given that stability over time is one of the most critical point for APIs as well as their pharmaceutical formulations, the tendency of **MT-o** to slowly recrystallize from its amorphous form must be taken into account when dealing with its pharmaceutical development. In particular this finding appears important when API solid forms (amorphous or crystalline) are assessed, discussed and related to different formulations and manufacturing processes in view of their pharmaceutical development.[62]

As for **MS**, the correspondence between bulk powder and single crystals was ascertained by comparing the experimental XRPD pattern collected at room temperature with the theoretical one obtained by using the SCXRD data of **MS-m** reported by Di Vaira[26] (see figure S10 in Supplementary Material).

MS-m does not change phase until melting (melting temperature: peak 410.4 K, extrapolated peak 410.8 K; melting enthalpy 175.4 J/g, 114.36 kJ/mol, from DSC measurements). These calorimetric data (the higher melting temperature parallels the higher melting enthalpy) suggest for **MS-m** a slight higher cohesive energy with respect to **MT-o**. After melting, during the cooling step, recrystallization to the starting form occurs (see figure S11), as shown by the diffraction profiles collected in the range 303-420-303 K (under N_2 atmosphere). In other words, the **MS-m** crystal phase appears stable with respect to a heating/melting/cooling sequence.

However, a detailed comparison of the diffractograms collected at different temperature (figure 12) highlighted that, upon heating, while there were no differences in the overall number of the peaks, as well as in their relative intensities, several peaks shifted towards lower 2ϑ values, unlike others that did not move significantly. The analysis of the collected diffraction patterns did not show significant shifts of the (h00), (00l) and (h0l) peaks upon temperature increasing (or cooling), on the contrary the (hk0) and (0kl) peaks shifted more evidently (see figure 12). This observation led us to postulate the occurrence of a reversible anisotropic lattice expansion/contraction along the *b* axis upon changing the temperature (see figure S11). The lattice parameters (table 4) calculated from the diffraction patterns (see Methods and materials section) and the linear thermal expansion coefficients (TECs,[63,64,65] Table 5) well support this hypothesis: the *b* axis significantly expands with respect to both *a* (whose expansion is negligible) and *c* (which even slightly contracts) axes.

The anisotropic expansion observed in **MS-m** prompted us to reassess its crystal packing in order to possibly find a hint for this behavior. The strong H-bonds along the *c* axis, already discussed, can account for the negligible variation of this cell axis upon temperature change. As for the other cell directions, weak CH···π interactions connect the metoprolol ribbons along both the *a* and *b* axes (see figure S7). However, when considering a possible lattice expansion, we reasoning that along the *a* axis this should cause a significant change in the orientation of the CH bond direction with respect to the mean plane of the aromatic ring (see table 3), while an expansion along the *b* direction seems less affecting such a good directionality (see table 3) and could be less dramatic in terms of molecular rearrangement (thus favoring the return to the original packing when the temperature decreases). Nevertheless, we are absolutely aware that this observation hardly suffices on its own to account for the anisotropic thermal behavior

observed, given that the stability of a crystal, and hence its response to an external stimulus (temperature, pressure, etc.), depends on a plethora of intermolecular interactions of both attractive and repulsive kind.[66]

Nonetheless, the anisotropic expansion/contraction observed for **MS-m** during the heating/cooling steps is an important point when the phase purity of the API, as well as its phase composition in formulations, is assessed by comparing powder diffraction patterns[67]. In fact, in addition to the expected discrepancies observed in the peak positions when comparing calculated XRPD patterns (from SCXRD data usually collected at low temperature) with experimental patterns (normally collected at room temperature), unexpected differences, arising from lattice expansion/contraction which affect in different extent the lattice parameters, as in **MS-m**, could lead to mistakes in identifying the phase composition.

Conclusions

In this paper we have presented a solid-state characterization of the tartrate and succinate metoprolol salts by using a combination of techniques (XRD by both single crystal and microcrystalline powder and DSC) in different experimental conditions, while the conformational space of the metoprolol-like molecule has been assessed by modeling.

Crystal structure analyses have revealed that in both salts the metoprolol cation interacts with the dicarboxylate anion *via* strong H-bonds, being the latter comparable in terms of donor-acceptor type, strength and number. This observation parallels the fact that the tartrate hydroxyl groupings are not involved in intermolecular contacts, that is tartrate and succinate anions are involved in the same kind of intermolecular H-bonds. In addition the tartrate and succinate salts have

comparable crystal densities, thus suggesting similar packing efficiencies (notwithstanding the higher number of weak interactions in **MT-o** with respect to **MS-m**). However, calorimetric data from DSC measures suggest for **MS-m** a slight higher cohesive energy with respect to **MT-o**, which cannot be accounted for by considering both strong and weak intermolecular interactions alone. On the other hand, the different effect of temperature on the lattice parameters of both **MS-m** (anisotropic lattice expansion/contraction) and **MT-o** (isotropic) cannot be fully explained by the network of intermolecular contacts which stabilize their crystal packing.

Finally upon cooling, while **MS-m** quickly re-crystallizes from its molten phase to the starting crystal phase, the strictly related **MT-o** gives an amorphous form and takes six days at ambient conditions to achieve complete re-crystallization to the original crystal form. As for this latter point, we wonder if, in the amorphous phase, the hydroxyl groups of the tartrate anions could play a role in altering the rate of crystallization of this salt with respect to the succinate one, due to their ability to form H-bonds. As a consequence the answer to the question "what really makes the difference between the crystal samples of **MS-m** and **MT-o** and possibly account for their "*macroscopic* different behavior" is still opens and proves once more the absolute necessity to perform a full solid state characterization especially when dealing with APIs.

As for the latter point, the results from the solid state studies as the temperature changes, i.e. the reversible crystalline-to amorphous-to crystalline phase transition of **MT-o** and the anisotropic lattice expansion observed for **MS-m,** are both relevant when dealing with the phase purity of these salts in the field of their pharmaceutical development.

FIGURES

Figure 1. ORTEP-3 representation of the two metoprolol cations in **MT-o** (enantiomer R is labelled with a and enantiomer S is labelled with b).

Figure 2. Superimposition of the R (ball and stick) and of the S (mirror plane-image, stick) of the two enantiomers of the metoprolol cation in **MT-o**.

Figure 3. Superimposition of the X-ray structures of the cationic species found in the CSD plus in **MT-o**. Structures are superimposed by "ball-and-stick" atoms. Hydrogen atoms have been omitted for clarity. Color key: **MS-m** = green; **MT-o** = red; JIRWIR = pale blue; CIMJUD = purple; QAJYIL = orange; DETHIU = brown.

Figure 4. Superimposition of the X-ray structures of the neutral species found in the CSD. Structures are superimposed by "ball-and-stick" atoms. Hydrogen atoms have been omitted for clarity. Color key: BEMBOK = pale green; CEZVIN = dark blue; CIDHAZ = green/fuchsia; GAPZEE = brown; KAZPOQ = turquoise; ROKNUB = black.

Figure 5. Superimposition of the X-ray structures of the cationic and neutral species. Structures are superimposed by "ball-and-stick" atoms. Hydrogen atoms have been omitted for clarity. For color key definition see figures 3 and 4.

Figure 6. Superimposition of the X-ray structures of the S enantiomer found in **MS-m** (green) and **MT-o** (red). Structures are superimposed by "ball-and-stick" atoms. Hydrogen atoms have been omitted for clarity

Figure 7. A) base-unit of ribbons in **MT-o** viewed along the c axis; B) chains of alternating R and S metoprolol cations paired by tartrate anions in **MT-o** viewed along the *b* axis.

Figure 8. Crystal packing of **MT-o** (view along the *b* axis).

Figure 9. Metoprolol succinate ribbons as present in the crystal packing of **MS-m**.

Figure 10. Superimposition of the XRPD patterns of **MT-o** collected at 173, 183, 213, 243, 273 K in vacuum (A) and 303, 323, 348, 373 K in air (B). In (B) for comparative purposes the XRPD patterns collected at 243 and 273 K in vacuum are also reported.

Figure 11. Superimposition of XRPD patterns of **MT-o** collected after the melting and then after four (top), six and fourteen days (bottom).

Figure 12. Superimposition of the XRPD patterns of compound **MS-m** at different temperatures (303, 323, 348 and 373 K).

SCHEMES

Scheme 1. Schematic drawing of the metoprolol molecule.

Scheme 2. (a) Fragment searched in the CSD; (b) model used in the modeling studies.

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TABLES.

Table 1. Crystallographic data and refinement parameters for **MT-o**.

Empirical formula	$C_{34}H_{56}N_2O_{12}$
Formula weight	684.80
T (K)	100
Crystal system, space group	orthorhombic, $P2_122_1$
λ (Å)	1.54184
Unit cell dimensions (Å)	a = 45.51(1) b = 8.484(2) c = 9.489(1)
Volume ($Å^3$)	3664(1)
Z, d_{calc}(g/cm^3)	4, 1.242
μ(mm^{-1})	0.774
Refinement method	Full-matrix least-squares on F^2
Reflections collected / unique	10032/3906 (Rint =0.0690)
Data / parameters / restrains	3906/428/6
Final R indices [I>2σ(I)]	R1 = 0.0671, wR2 = 0.1569
R indices (all data)	R1 = 0.1360, wR2 = 0.1967

Table 2. Main torsion angles (°), obtained from X-ray diffraction studies, defining the overall shape of the S enantiomer of metoprolol cations in **MS-m**, **MT-o** and **MT-m**.

Dihedral Angles (°)	**MS-m**[1]	**MT-o**	**MT-m** [2]
C(2)-C(1)-O(1)-C(7)	1.48(1)[3]	10(3)	10/9
C(1)-O(1)-C(7)-C(8)	-177.6(1)	167(1)	166/169
O(1)-C(7)-C(8)-C(9)	-65.1(2)	-174(1)	-171/-169

C(7)-C(8)-C(9)-N(1)	166.9(1)	156(1)	161/158
C(8)-C(9)-N(1)-C(10)	172.0(1)	176(1)	177/176
C(9)-N(1)-C(10)-C(11)	177.5(1)	166(1)	165/171
C(15)-O(3)-C(14)-C(13)	-170.6(2)	-174(1)	-177/-175
O(3)-C(14)-C(13)-C(4)	175.1(1)	-173.(1)	-177/-175
C(14)-C(13)-C(4)-C(3)	52.5(2)	-96(2)	-91/-89

[1]From ref. 26, angular values refer to the S cation found in the crystal lattice.

[2]From ref. 14, angular values refer to the two independent S cations found in the crystal lattice.

[3]Value refers to the C(6)-C(1)-O(1)-C(7) in the Di Vaira paper.[26]

Table 3. Selected intermolecular interactions in **MS-m**[26] and **MT-o**.

Strong H-bonds

MS-m		**MT-o**	
	X···Y (Å) - H···Y (Å) – X-H···Y (°)		X···Y (Å) - H···Y (Å) – X-H···Y (°)
N-H(1N)···O(5)[1]	2.745(2) – 1.85 – 162	N(1a)-H(1a2)···O(5a)	2.73(2) – 1.92 – 150
		N(1b)-H(1b2)···O(5b)	2.78(2) – 1.93 – 160
N-H(2N)···O(4)[2]	2.796(2) – 1.89 – 170	N(1a)-H(1a1)···O(4b)[3]	2.70(2) – 1.85 – 157
		N(1b)-H(1b1)···O(4a)	2.85(2) – 1.99 – 165
O(2)-H(2O)···O(4)[1]	2.723(2) – 1.88 – 179	O(2a)-H(2a)···O(4a)	2.58(2) – 2.00 – 128
		O(2b)-H(2b)···O(4b)	2.68(1) – 2.19 – 119

[1] x, -y, z-1/2; [2] –x+1, y, -z+3/2; [3] x, y, z-1

Weak interactions

C-H...π interactions in **Ms-m** (data from ref.26)			
	H···CT[4] (Å)	C-H···CT (°)	H-CT/(C1-C6)$_{mean\ plane}$ (°)
C(13)-H(132)···CT[5]	2.79	160	82

C(14)-H(142)···CT[6]	2.84	157	81
Weak H-bonds in **MT-o**			
X-H···Y	X···Y (Å)	H···Y (Å)	X-H···Y (°)
C(11a)-H(11c)···O(5b)[7]	3.32(3)	2.40	160
C(13a)-H(13b)-O(3b)[8]	3.70(2)	2.83	149
C(3a)-H(3a)-O(3b)[8]	3.44(2)	2.59	152
C(12b)-H(12e)···O(5a)[9]	3.65(2)	2.77	155
C(3b)-H(3b)-O(3a)[10]	3.44(2)	2.58	153
C(13b)-H(13d)-O(3a)[10]	3.56(2)	2.66	154

[4]CT is the centroid of the C1-C6 aromatic ring; [5] = -x+1/2,+y-1/2,-z+3/2; [6] = -x+1/2,+y+1/2,-z+3/2; [7] x, y-1, z-1; [8]-x+3/2, -y, z-1/2
; [9] x, y+1, z; [10] -x+3/2, -y+1, z+1/2.

Table 4. Cell parameter for **MS-m** at different temperature from XRPD data.

	a(Å)	*b(Å)*	*c(Å)*	*β(°)*	V*(Å³)*	Rwp
200K	26.30(2)	7.980(6)	17.54(2)	107.31(5)	3514.4(1)	8.61
273K	26.33(2)	8.077(6)	17.51(2)	107.31(5)	3555.2(1)	8.43
298K	26.34(2)	8.121(5)	17.50(2)	107.27(6)	3574.6(1)	8.81
323K	26.36(2)	8.160(4)	17.48(2)	107.27(6)	3590.4(1)	8.73
348K	26.36(2)	8.200(3)	17.46(2)	107.35(7)	3602.3(1)	8.63
373K	26.41(2)	8.259(3)	17.46(2)	107.32(6)	3635.7(1)	8.62
393K	26.45(2)	8.300(4)	17.46(2)	107.40(8)	3657.7(1)	8.64

Table 5. Linear (α) and volume (β) thermal expansion coefficients (TECs)[63] calculated for **MS-m** taking as reference the cell parameter values calculated at 200K.

T(K)	$\alpha a(10^{-5})\,C^{-1}$	$\alpha b(10^{-5})\,C^{-1}$	$\alpha c(10^{-5})\,C^{-1}$	$\beta(10^{-4})\,C^{-1}$

200				
273	1.6	16.7	-2.3	1.6
298	1.6	18.0	-2.3	1.8
323	1.9	18.3	-2.8	1.8
348	1.5	18.6	-3.1	1.7
373	2.4	20.2	-2.6	2.0
393	3.0	20.8	-2.4	2.1

ASSOCIATED CONTENT

Supporting Information. Table with intramolecular interactions, NMR spectra, additional XRPD patterns and DSC curve, dihedral angle plots and figure from MD traectories. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic information file is also available from the Cambridge Crystallographic Data Center (CCDC) upon request (http://www.ccdc.cam.ac.uk, CCDC deposition numbers 1425892).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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